

# Cancer in Inflammatory Bowel Disease

ADRIAN J. GREENSTEIN, M.D., F.A.C.S., F.R.C.S.

## Abstract

The first case of cancer in inflammatory bowel disease (IBD) was reported at The Mount Sinai Hospital in 1925 in a patient with ulcerative colitis (UC). In 1956, carcinoma of the jejunum was described in a patient with regional enteritis (Crohn's disease [CD]). IBD cancers are preceded by dysplasia, and the relative risk increases with duration of the IBD. CD cancers are more proximally distributed than are UC cancers. Both tend to occur at the site of the overt disease and both develop at earlier ages (47 UC, 50 CD) than in the *de novo* colorectal cancer (70 years).

The absolute cumulative colon cancer frequencies (8% UC, 7% CD) are identical after 20 years, emphasizing the importance of regular surveillance in both types of IBD. Moreover, the increased risk of colon cancer exists in patients with CD even when CD is confined to the small bowel, and patients with IBD have increased risks of developing extraintestinal and reticuloendothelial tumors in both CD and UC, as well as ano-vulval and malignant melanoma in CD. Colitic colorectal cancers are often diffuse, extensive, multiple and right-sided with insidious presentation. The prognosis is no worse after operation than that of *de novo* colon cancer.

Most small bowel cancers in CD are adenocarcinomas, rather than sarcomas, and present at a younger age, more diffusely and more distally than *de novo* cancers, usually making them undiagnosable at a curable early stage; indeed, two-thirds present with intestinal obstruction. Strictures of the colon are common in patients with IBD, and they have a 10-fold risk for colon cancer, 30-fold for UC, and 6-fold for CD. The risk increases with disease duration. The indications for surgery are absolute, relative and incidental, and the procedures include segmental resection, total proctocolectomy, subtotal colectomy and palliative procedures.

**Key Words:** Inflammatory bowel disease, cancer.

---

WE OBSERVED IN ONE CASE a malignant degeneration of the late stage of polypoid ulcerative colitis, with the frank occurrence of carcinoma of the rectal wall. In brief this was a case of nonspecific ulcerative colitis of the colon 14 years in duration. The polypoid stage was already in evidence 10 years ago. More recently the patient came under observation with renewed symptoms of his disease. The sigmoidoscopic examination revealed an extensive polypoid colitis, in addition to which one observed on the left lateral wall of the rectal ampulla, growing in a mass of polypoid excrescences, an ulcerating massive neoplasm. Section removed for histological

examination revealed the presence of an adenocarcinoma. (1)

## Historical Background

For more than 70 years, surgeons and gastroenterologists at The Mount Sinai Hospital have been intrigued by the association of cancer with inflammatory bowel disease. Although Crohn is known for his description of regional ileitis, the first case of cancer in inflammatory bowel disease reported and described was actually one of ulcerative colitis-associated rectal cancer (see above) by Crohn and Rosenberg in 1925 (1). This was 66 years after the classic description of ulcerative colitis by Sir Samuel Wilks in 1859 (2). Since then, many reports have appeared confirming the high incidence of cancer of the large bowel in cases of ulcerative colitis, particularly for those with longstanding universal disease (3–5). The occurrence and significance of cancer in Crohn's

---

From the Department of Surgery, Mount Sinai School of Medicine, New York, NY.

Address correspondence to Adrian J. Greenstein, M.D., Mount Sinai School of Medicine, Department of Surgery, Box 1259, One East 100th Street, New York, NY 10029.

disease were not appreciated until many years after the classic description of regional enteritis by Crohn, Ginzburg, and Oppenheimer was published in 1932 (6). Carcinoma occurring in association with Crohn's disease was first recognized in the large bowel (7), then in the small bowel (8) (see below), and subsequently at extraintestinal locations (9).

Dr. Leon Ginzburg et al. described a case of "carcinoma of the jejunum occurring in a case of regional enteritis" in 1956 (8):

This was believed to be the first report of carcinoma arising in the small intestine at the site of stenosing granulomatous enteritis. From the age of 11 until 30 this patient had been subjected to frequent bouts of crampy abdominal pain, with marked but non-bloody diarrhea, followed by relative constipation. In October of 1952 a gastrointestinal series revealed rigidity of the segments of small bowel involving the jejunum, with areas of dilatation between. A diagnosis of ileojejunitis was made. He was admitted with acute intestinal obstruction. Physical examination revealed a thin patient with distended abdomen and visible peristalsis, and hyperactive peristaltic rushes on auscultation. The entire segment from 18" to 6 feet from the ligament of Treitz, with multiple strictures, was resected. The tumor mass 40 cms from the proximal end consisted of an adenocarcinoma arising from the mucosa and invading the bowel wall. Cords of anaplastic cells invaded the serosa. Seven months later the patient was readmitted with widespread metastatic disease also involving the liver.

This case report describes a typical case of carcinoma occurring in stricturing small bowel disease. We have seen patients with cancer-complicating stricturing disease.

For several decades following the early description of granulomatous disease of the bowel by Dalziel in 1913 (10) and its fuller elucidation by Crohn, Ginzburg, and Oppenheimer in 1932 (6), it was generally accepted that cancer did not occur with Crohn's disease. There were no reports of cancer until 1948, when Warren and Sommers described the first case of carcinoma of the large bowel occurring in association with Crohn's disease (7). The number of described cases has increased dramatically over the last few decades. There are now considerably more than 128 patients in whom cancer of the large bowel has been reported in association

with Crohn's colitis, ileocolitis, and even regional enteritis (11).

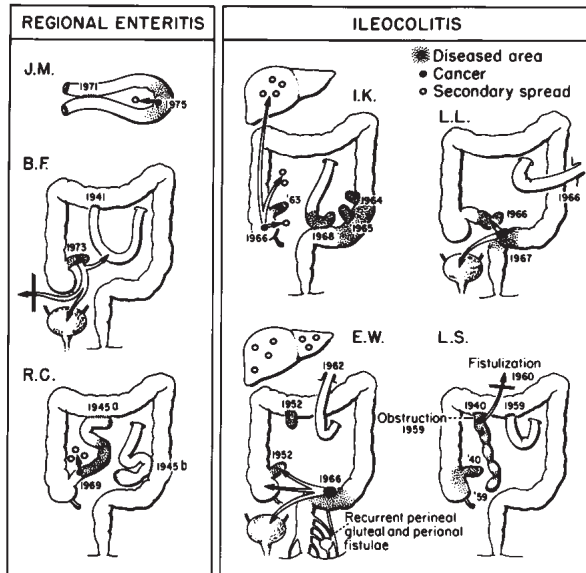
The first reports of cancer occurring in the jejunum in patients with regional ileitis and jejunitis were those of Ginzburg et al. (8) and Kornfeld, Ginzburg and Adlersberg (12). These authors described the following case.

A 36-year-old white woman was admitted to The Mount Sinai Hospital in 1955. She was suffering from upper abdominal pain, persistent vomiting, loss of weight and marked weakness. Her initial gastrointestinal symptoms, characterized mainly by severe diarrhea, were first manifested eight years previously. At that time she was admitted to another institution where radiological studies revealed evidence of colitis. She continued to have four or five watery bowel movements daily which never showed evidence of blood pus or unusual quantities of mucus. Her weight fell from 125 to 75 pounds. She was treated by one of us with Aureomycin and cortisone and regained 40 pounds in weight in a few months. Despite radiologically demonstrable widespread disease she remained actively employed for five years. An obstructive episode was treated by suction and followed by four months of medical treatment. Radiologic studies revealed dilated jejunum and a rigid segment. She was readmitted with obstruction and found to have an unresectable jejunal mass and multiple areas of disease. She died with metastatic liver disease six months after a retrocolic duodenojejunal bypass.

Since this time, more than 80 cases of cancer of the small bowel have been reported in patients with Crohn's disease (13–15). Among these cases, 17 have occurred in excluded segments of bowel (13, 16–18), of which 7 cases have been reported from this hospital (Fig. 1) (19).

Brown, Weinstein and Janowitz (16) described a "carcinoma of the ileum 25 years after bypass for regional enteritis" in 1970. This 55-year-old woman was admitted to The Mount Sinai Hospital in 1969. Twenty-five years earlier, she had developed low abdominal pain and fever. At laparotomy 6 months later, Crohn's ileitis was found and an ileotransverse colostomy was constructed. Because of obstruction, this was revised to a side-to-side ileodescending colostomy (see Fig. 1, case 3 RC), leaving the proximal colon in place. At re-exploration, the terminal ileum and cecum were resected and an adenocarcinoma with two positive lymph

### BYPASS PROCEDURES IN SEVEN PATIENTS WITH CANCER IN EXCLUDED SEGMENTS



**Fig. 1.** Bypass procedures in seven patients with cancer in excluded segments.

JM = metastasizing cancer in jejunum four years after side-to-side jejunioileal bypass in-continuity.

BF = fistulizing cancer in terminal ileum thirty-three years after ileotransverse colostomy with exclusion.

RC = locally metastasizing cancer in terminal ileum twenty-five years after ileodescending colostomy with exclusion.

IK = metastasizing cancer in uninvolved cecum four years after diverting ileostomy and subsequent ileosigmoid bypass of terminal ileum.

LL = fistulizing cancer in diseased sigmoid colon two years after diverting ileostomy.

EW = fistulizing metastatic mixed mesodermal sarcoma in diseased sigmoid colon fourteen years after exclusion bypass of terminal ileum and four years after diverting ileostomy.

LS = cancer in multiply strictured segment of ileum, occurring at site of nineteen-year-old ileotransverse colostomy, and discovered upon malignant fistulization after secondary bypass.

Reprinted from reference #19 with permission.

nodes was found. She developed a subphrenic abscess and died on the 31st postoperative day.

### General Considerations

It is generally accepted that the numbers of cases of inflammatory bowel disease (IBD)-associated cancer in the colon in ulcerative colitis (UC) and in the small bowel in Crohn's disease (CD) have increased. The question of the colorectal cancer (CRC) risk in Crohn's disease remains controversial and will be discussed in detail below. Early reports suggested a poor prognosis for all gastrointestinal cancers in inflammatory bowel disease, but recent studies of larger series of patients have indicated a better

prognosis, especially in patients with colitic colorectal cancer. In these patients, survival is similar to that in non-colitic CRC.

### Clinico-Pathologic Features of IBD Cancer

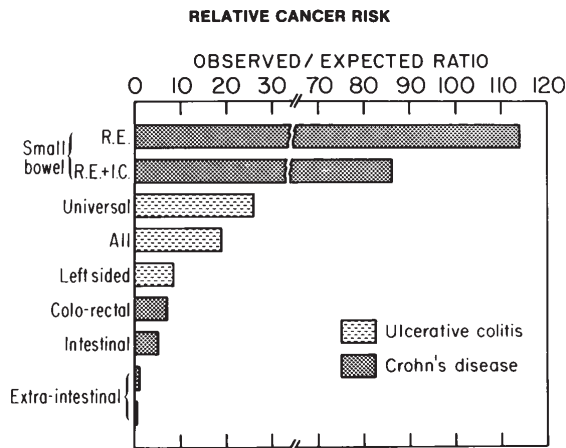
Cancers occurring in IBD differ in many respects from those occurring *de novo*. In general, they occur earlier in life; the anatomic distribution is different, being influenced by sites of disease; and they are more frequently multiple and mucinous. The cancer risk is greater than in the general population (Fig. 2), and increases with longer disease duration (Fig. 3). In both diseases, cancer is preceded by dysplasia, which allows for surveillance for colorectal cancers. Both ulcerative colitis CRC (UCCRC) and Crohn's disease colorectal cancer (CDCRC) occur in association with strictures, although UC strictures are more frequently malignant.

Cancers occurring in CD, although similar in many respects, differ in some respects from those developing in UC. CD cancers have a more proximal distribution; may occur throughout the gastrointestinal tract, since CD is a diffuse disease; and may occur in association with fistulas or excluded loops. In both diseases, cancers tend to occur at sites of overt disease. In CDCRC, cancers may occur in normal-appearing bowel in as many as one-third of patients (20). We have recently described six patients (a seventh has been seen more recently) with Crohn's disease limited to the small bowel, who developed cancers of the colon and rectum (21). These observations of a wide distribution of cancer within the intestinal tract, as well as the occurrence of diffusely infiltrating (22) and multiple (23) cancers, are consistent with the fact that Crohn's disease may affect the whole gastrointestinal tract, even in the absence of overt disease (24–27). Furthermore, recent endoscopic studies have shown that one-third of patients with Crohn's disease, and even some patients incorrectly diagnosed as having ulcerative colitis, have macroscopic or histologic evidence of involvement of the upper gastrointestinal tract in the absence of any radiologic changes (28). Each of the above features of cancer in CD will be considered in detail below.

### Cancer Risk

#### Overall Risk

Several studies have suggested an increased incidence of gastrointestinal cancer in patients

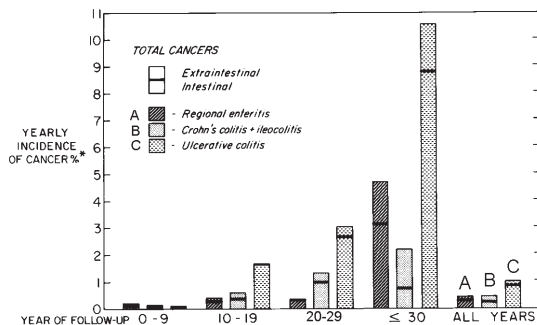


**Fig. 2.** Relative cancer risk in patients with ulcerative colitis and Crohn's disease.

R.E. = Regional Enteritis.

I.C. = Ileocolitis.

Universal = universal colitis involving all segments of colon and rectum.



**Fig. 3.** Incidence of gastrointestinal cancer in Crohn's disease and ulcerative colitis for patient years at risk starting from onset of first symptoms. The cancer risk increases progressively with each passing decade for all categories of inflammatory bowel disease, but the absolute incidence rates are three times higher in ulcerative colitis than in Crohn's disease.

Bars:

A = Regional enteritis — left bars

B = Crohn's colitis + ileocolitis — middle bars

C = Ulcerative colitis — right bars

For each decade of follow up, Extraintestinal yearly incidence, in percent, is indicated by the amount above the horizontal line within each bar, while the yearly incidence, in percent, for Intestinal cancer is indicated below the horizontal line.

with Crohn's disease. Fielding et al., in 1972, found seven cancers in the gastrointestinal tract, including two in the pancreas and two in the small bowel (29). Alexander-Williams' 1976 series of 12 gastrointestinal cancers among 500 patients with Crohn's disease also included higher than expected numbers of cancers in small bowel, large bowel, esophagus, and pancreas (30). Similarly, our 1979 study of Mount Sinai patients revealed an increased incidence of both small and large bowel cancers when compared

with an age- and sex-matched population (Fig. 3) (5). The incidence of gastrointestinal cancer in Crohn's disease increased with disease duration in a way similar to that in ulcerative colitis (Fig. 3) (14).

### Colorectal Cancer Risk in Colitis

The risk of colorectal cancer is considerably increased for patients with ulcerative colitis, particularly for those with universal disease (all segments of colon and rectum) of long standing (7-9, 31). The overall incidences of ulcerative colitis-associated colorectal cancers (fewer than 1,000 per year in the United States) and of Crohn's colitis (less than 100 per year) are not high when compared with the total yearly incidence of 140,000 for colorectal cancers in the general population. Nevertheless, the issue of colorectal cancer risk in inflammatory bowel disease must take into account a number of important factors. First, the relative risk of colorectal cancer is much increased in age- and sex-matched populations in both ulcerative colitis and Crohn's colitis. Second, both forms of colitis colorectal cancer occur in patients younger than in *de novo* colorectal cancer. The mean age at development of cancer is approximately 56 years for Crohn's colitis and 49 years for ulcerative colitis, compared with 70 for *de novo* colorectal cancer (32). Third, since colitis colorectal cancer is a premalignant condition, cancer could theoretically be prevented in both UCCRC and CDCRC if high-risk cases could be identified early, so that timely colectomy could be carried out.

There is much controversy regarding the incidence of colorectal carcinoma with Crohn's disease. A high incidence was reported in two early publications from England. In 1965, Atwell et al. in Leeds reported three colorectal cancers among 62 patients, an incidence of 5% (33). Then, in 1968, Perrett et al. in Oxford found three cases among 82 patients with Crohn's disease, a 4% incidence (34). Although other series failed to confirm as high an incidence, Weedon et al. at the Mayo Clinic found that their patients with Crohn's colitis, whose disease onset occurred before 21 years of age, had an incidence of colorectal cancer 20 times higher than expected (35). The seven colorectal cancers in our early series of 327 patients (2%) with Crohn's colitis or ileocolitis represented an increased incidence of about 7 times what was expected (14). We now have a collected series of 30 (3 multiple) colorectal cancers among our patients with Crohn's disease. Eight large bowel cancers occurred in seven

patients with regional enteritis and 25 among 23 patients with colitis and ileocolitis.

Warren and Sommers reported the first case of adenocarcinoma complicating Crohn's disease in 1948 (7). For the next 30 years, reports of single (22, 36), and even multiple cases (23, 33, 35–38), failed to dispel the skepticism surrounding this association. More recent studies, however, have clearly demonstrated the increased risk of colorectal cancer for those patients with Crohn's disease who have extensive, longstanding, unresected colonic involvement (14, 20, 39, 40). Nevertheless, the association between Crohn's disease and colorectal cancer remains controversial, with a number of doctors disputing the association (41–45). However, each of these five populations-based studies calculated their relative risks without specific regard to the population actually at risk; namely, patients with "extensive, longstanding, unresected" colonic disease. All of these studies show an increase in relative risk of approximately 10-fold if corrected for these factors (46). A recent study from Birmingham compared the cancer risk between two hospital-referred but identically selected cohorts of patients with extensive ulcerative colitis and equally extensive Crohn's colitis (40). This study established a virtually-identical, absolute, cumulative frequency of 7% and 8%, for CD and UC respectively, at 20 years, thereby confirming the previously noted similarities between cancer incidences in these two diseases (14, 20, 39). In their prior 1994 study (47), Gillen et al. found that the relative risk of 4.9 for colorectal cancer increased to 13.3 for patients younger than 25 years of age at onset of CD, and to 18.2 if corrected for extensive colitis. If both factors were present, the risk rose to 57.2. Thus, in the presence of longstanding, extensive disease and unresected colon (this would seem to be obvious, but many authors have failed to exclude patients who have "no colon" and therefore are at "no risk!"), especially with early onset of Crohn's disease, the risk clearly is increased. In these high risk patients, it could be argued that as in ulcerative colitis regular surveillance should be carried out.

### **Colorectal Cancer Risk in Regional Enteritis**

One question that remains unresolved is the possible association between colorectal carcinoma and small bowel Crohn's disease (42, 48). Even though seven (23%) of our patients, five of whom were previously reported (15, 21), had overt Crohn's disease confined to the small

bowel, they nonetheless developed eight carcinomas. Five of these occurred in the colon and three in the rectum. It could be argued that colorectal cancer, being a common disease, appeared only coincidentally in two patients, both of whom were more than 60 years of age, with short duration disease at the time of cancer diagnosis. However, three of the seven ileitis cases presented with colorectal cancers, at ages 34, 38, and 42, suggesting a true increase in risk, and two developed cancer after 30 and 31 years of disease, at ages 70 and 78 respectively. Moreover, there were no significant differences in age at onset of Crohn's disease, age at cancer, and duration of disease to cancer, between patients with ileitis and those with either ileocolitis or colitis. This finding once again raises the question of whether small bowel Crohn's disease even predisposes someone to colorectal adenocarcinoma (42, 48), which would be consistent with the panenteric nature of this disease.

### **Extraintestinal Cancer Risk**

Although several studies prior to 1983 failed to demonstrate a statistically significant increase in incidence for extraintestinal cancers in patients with inflammatory bowel disease (14, 20, 38, 49), a more recent study of 2,000 patients with inflammatory bowel disease has shown an increase in three specific tumor groups in patients with either Crohn's disease or ulcerative colitis (4). The first group includes reticuloendothelial tumors: leukemias in ulcerative colitis (50, 51) and lymphomas in both ulcerative colitis and Crohn's disease (4, 52). The second group comprises tumors arising from chronic perineal inflammation in Crohn's disease: squamous carcinomas of the anus and vulva (4, 53). Finally, there may be an increased incidence of malignant melanoma in Crohn's disease (4, 54). It remains to be seen whether an increased risk of any of these cancers, some of which are similar to the types that occur in immunosuppressed and/or irradiated patients (55), can be documented in other medical centers.

### **Colorectal Cancer**

**Clinicopathological Features:** Colitic colorectal cancers show characteristic clinico-pathological features that tend to distinguish them from other colorectal cancers. They are more diffuse, not infrequently extending over more than one segment of bowel. They may be invisible to the naked eye, or they may infiltrate the bowel wall causing stricture formation. They are frequently

multiple, and the incidence of right-sided cancer is greater in colitis-associated than in *de novo* colorectal cancer, due largely to right-sided disease in CD and to the increased incidence of multiple synchronous cancers (32).

Cancers in colitis and regional enteritis have the unfortunate tendency of developing without giving clinical evidence of their presence in their early stages. Advanced cases are characterized by obstructive symptoms, rapid weight loss, and abdominal masses. Colorectal cancers in Crohn's disease may occur in excluded distal bowel or in association with enterovesical or colovesical (Fig. 1) (19, 56), rectovaginal (57, 58), colcutaneous (19, 59), or perianal fistulas (19, 53, 60). Crohn's disease colorectal cancers share some features with ulcerative colitis colorectal cancers. The clinicopathological features of colorectal cancer occurring in Crohn's disease, as in UC, are difficult to differentiate from the clinical features of the underlying inflammatory bowel disease. Compared to *de novo* cases, colorectal cancers in Crohn's disease occur at an earlier age (48 vs. 70 years), are more often located in the right colon (45%), and are more frequently multiple (22, 23). Multiplicity is less of a feature than in UCCRC where the incidence of multiplicity is reported to be 14–40%, compared with 4% for *de novo* colorectal cancer (32). It has been suggested that there are two separate populations among these patients. First, there are those with onset of Crohn's disease at older than 60 years of age, in whom the vast majority have had a relatively short duration of disease and in whom the Crohn's disease and cancer symptoms occurred simultaneously. This group, for example, constitutes approximately 20% of the patients in Hamilton's series (61). The second and much larger group consists of younger patients, usually with a long duration of disease. Examination of the literature prior to 1985 reveals that for all 29 patients younger than 60 years of age, for whom the duration of disease is recorded, the mean disease duration was 15 years, while for the 29 patients older than 60 years of age, the mean disease duration was 5 years. This thesis regarding two populations has been supported by a recent publication by Kyle and Ewen, who describe two such separate populations among patients in their area who developed Crohn's colorectal carcinoma (62). However, in Hamilton's series, there are also three older patients with long disease durations of 36–51 years, suggesting a third group with both older onset age and longer pre-existing disease duration (61). Six patients with onset of the disease after 70 years of age had a mean disease

duration of 25 years, but two elderly patients had simultaneous onsets of Crohn's disease and cancer at ages of 68 and 72, as first described by Hamilton (61). Since onset age of Crohn's disease in the sixth decade of life is unusual and the incidence of spontaneous colorectal cancer increased in late decades, patients in this latter group could represent either coincidental spontaneous cancer or colitis-associated cancers in a setting of long-standing, undiagnosed Crohn's disease.

### Cancer of the Small Bowel

**Clinicopathological Features:** Most cancers of the small bowel in Crohn's disease are adenocarcinomas, usually in the terminal ileum or jejunum; they are difficult if not impossible to diagnose at a curable stage. They differ from *de novo* cancers of the small bowel in many respects (13, 63). There is a lower average age at diagnosis of cancer in Crohn's disease, 45 years vs. 60 years; the site of cancer is more distal, 76% vs. 20%; and the mean postoperative survival time is less, 8 months vs. 32 months. Furthermore, sarcoma is an extremely rare form of small bowel cancer in Crohn's disease, whereas approximately one-third of *de novo* small bowel cancers are of this variety. There is also an increase in the proportion of multifocal or diffuse cancers in association with Crohn's disease. As with ulcerative and Crohn's colitis, the incidence of cancer increases with longstanding duration of Crohn's disease (Fig. 3).

In our 18 patients with known sites of intestinal cancer, the mean duration of Crohn's disease was 22 years (18 years for cancers occurring in bowel in-continuity and 28 years for cancers occurring in excluded bowel) (19). Hoffman et al. have reported similar figures, with 90% of their cases lasting more than five years, 70% more than ten years, and 38% more than 20 years from the onset of disease, yielding a mean disease duration of 18 years (63). Although the majority of cancers of the small bowel occur after a long duration of disease, Fresco et al. have drawn attention to the fact that as many as one-third of all cases may occur within the first decade of disease (64). However, the total number of patients at risk in the early onset group is much greater than in subsequent decades; hence the true cancer risk is much lower.

The most common clinical presentation of small bowel cancer is intestinal obstruction. This occurred in two-thirds of our patients (19). Other important symptoms include diarrhea, weight loss, abdominal mass, and abdominal fistulae (15,

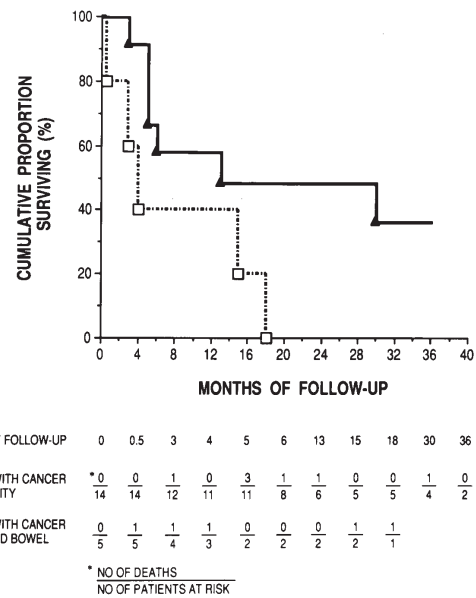
37). These symptoms are also found in Crohn's disease without cancer. The possibility of the development of complicating cancer should be entertained if the development of these clinical features follows "a long quiescent period" (19). Small bowel cancer is rarely suspected preoperatively, the diagnosis being made in fewer than 5% of reported patients, and in only two of our nineteen. Intraoperative, postoperative and autopsy diagnoses were made in 27%, 61%, and 7% respectively, of those 44 patients reviewed by Hoffman et al., for whom the timing of the diagnosis could be determined (63).

Three key microscopic features were described by Fleming and Pollock: invisibility, mucosal dysplasia, and endometriosis-like invasion of the stroma (65). Invisibility is defined as microscopic recognition when the cancer is difficult to perceive, even on opening the operative specimen. Mucosal dysplasia, similar to that originally described by Morson and Pang in ulcerative colitis (66), is found in 25% or more of cases of CDCRC (65, 67, 68) and suggests that surveillance should be carried out in selected cases with Crohn's disease.

The prognosis of carcinoma of the small bowel in Crohn's disease is poor. Among the 44 patients reported by Hoffman et al. (63), there were only two 5-year survivors (5%), compared with the 20–30% 5-year survival rate for *de novo* small bowel cancers. The mean postoperative survival time in those Crohn's disease patients who survived surgery was only 7.8 months. All of the small bowel cancers initially reported by Greenstein et al. (14) were fatal. However, in a larger series reported more recently, although all of the five patients with cancer in excluded bowel died within 18 months, the overall survival rate at three years was 23% (Fig. 4) (15). The survival rate of more than 30% at three years for in-continuity cancer was similar to that for *de novo* small bowel cancer. The prognosis for large bowel cancers is better. With colonoscopy today, we can expect an increased and earlier preoperative detection of colorectal cancer in Crohn's disease, and thus possibly a better prognosis for the large bowel variety, but not for that in the small bowel. Small bowel enteroscopy and push enteroscopy can now be tried but there is no proof of their diagnostic value.

### Strictures and Cancer

Enteric strictures are one of the common complications of Crohn's disease and are caused by marked thickening of the bowel secondary to



**Fig. 4.** Survival curves for five patients with cancer in excluded bowel and 14 patients with cancer in non-excluded bowel. The difference did not reach statistical significance. Reprinted from reference #15 with permission.

intramural fibrotic change. The frequency of benign colorectal strictures in Crohn's disease, and the difficulty of differentiating them from malignant strictures (Figs. 5 A, B, C), makes this a topic of major importance in the attempt to diagnose cancers at an early and curable stage. Although strictures occur more frequently in the small intestine than in the colon, 5–17% of patients with colonic Crohn's disease have a colorectal stricture. One hundred thirty-two of 980 patients (13.5%) with CD involving the colon, admitted to The Mount Sinai Hospital between 1959 and 1985, developed 175 colonic strictures (69). Thirty-three patients developed more than one stricture. The frequency was twice as great in colitis (19%) as in ileo-colitis (11%). Ten malignant strictures were identified in 9 patients (3 ileocolitis, 6 colitis). One of these patients had three strictures (2 malignant and 1 benign), and two had 2 strictures (1 malignant and 1 benign).

The frequency of cancer in patients with stricture (6.8%) was higher than in those without stricture (0.7%, 6 of 848,  $p < 0.001$ ). There were no differences in clinical symptoms between patients with benign and malignant stricture. Seventeen of 165 benign strictures (10.3%) were long, extending over more than one anatomical segment of colon, but all ten malignant strictures were short ( $p < 0.0001$ ).

The age at the diagnosis of stricture was significantly higher in the 9 patients with malignant stricture than in the 123 patients with benign



**Fig. 5.** Malignant and benign strictures in inflammatory bowel disease.

**A.** Malignant stricture in ulcerative colitis in which the cancer was missed for a year after endoscopy failed to pass the stricture.

**B.** Benign stricture in Crohn's disease in which malignancy was suspected.

**C.** Thirty-five-year-old woman who had Crohn's colitis for 20 years. She developed multiple colonic cancers. Only the malignant stricture of the transverse colon is readily apparent in this X-ray. She survived for five years following chemotherapy despite transmural metastases found at laparotomy.

stricture (mean age 57.2 vs. 41.4 years, respectively,  $p < 0.01$ ). The proportion of strictures that were malignant increased with duration of disease, from 3.3% with less than 20 years of CD, to 11% with CD of 20 years or more. All nine patients with malignant stricture were treated surgically, and 4 of the 9 died of colon cancer during a mean follow up of 4.3 years. In view of the high rate of malignancy, 6.8%, in this series, colonoscopy with biopsy is essential in Crohn's disease patients with colonic strictures, and surgery is mandatory when a stricture cannot be

fully assessed during colonoscopy. Unlike ulcerative colitis, in which proctocolectomy is required, in segmental Crohn's disease, a more limited segmental resection may be appropriate treatment in some patients. Follow-up surveillance is essential in these patients.

The frequency of colon cancer in stricture patients was 10 times higher than in non-stricture patients in our series. Although there appears to be an association between colorectal cancer and stricture, it is not clear whether benign strictures degenerate into malignancy or whether cancers present as strictures. The proportion of malignant strictures increased with increasing duration of Crohn's disease (Fig. 2). This observation is consistent with the fact that longer duration of disease is associated with increased risk of colorectal cancer, with or without stricture. Malignant disease must be ruled out if a stricture is found in a patient with Crohn's (ileo)colitis. Radiological examination is of value for detection of colonic stricture, but is not reliable for the differentiation of benign from malignant disease. Following radiological detection of a stricture, endoscopy with biopsies throughout of the length of the stricture is essential. Multiple biopsies should be taken at the proximal and distal edges, and from within the stricture, in order to rule out dysplasia, carcinoma *in situ*, or frank adenocarcinoma. Surgery must be considered whenever the endoscopist cannot visualize the entire length of the stricture.

As in Crohn's disease, any patient with ulcerative colitis who develops a stricture or obstruction should immediately be evaluated by colonoscopy. The risk of cancer is even greater in UC strictures. Gumaste et al. found that 17 of 58 patients with colorectal strictures in UC had malignant strictures (70). Seven of these 17 patients with malignant strictures in ulcerative colitis presented with partial or complete obstruction, compared with none of 42 with benign strictures. In both Crohn's disease and ulcerative colitis, a remarkable degree of narrowing, sometimes to as small as one to two millimeters, can occur without the development of obstructive symptoms, which must be attributed to the liquidity of the stool.

### Surveillance of Crohn's Disease for Carcinoma

Surveillance for cancer in patients with Crohn's disease remains controversial, but should seriously be considered for selected groups of patients who are at a high risk for the development of colorectal cancer. In the 1980s, Korelitz (71, 72), and Shorter (73) suggested the need for

surveillance, while Butt (74, 75), Fielding (29), and Warren (7) did not advise prophylactic measures, but they recommended "vigilance." In 1985, Hamilton (61) suggested that cost-benefit studies of surveillance protocols were needed in well-defined Crohn's disease populations.

Several factors make it difficult to propose a rational surveillance program for Crohn's disease patients. These factors include the variety of cancers which occur in association with Crohn's disease: extraintestinal (4) and intestinal (14), small bowel (3, 13, 15, 18, 64), and large bowel (2, 35, 61, 68). There are also several different modes of clinical presentation: cancers following long duration of disease (3), cancers coincident with onset of Crohn's disease (34, 37, 61, 67), cancers remote from overt disease (13, 14, 61, 76), and cancers in excluded segments (19). Finally, there are features that make the diagnosis difficult to establish even when a lesion is suspected and sought: the inaccessibility of small bowel to endoscopic examination, the difficulty of evaluating segments of bowel that are either bypassed (16, 18, 19, 77) or proximal to strictures (4, 69, 78), the "invisibility" (65) or "occult" (67) nature of the neoplasms, and the confounding of cancer symptoms with those of the underlying bowel disease.

I have proposed that regular clinical checkups should be instituted for patients with Crohn's disease, including examination of the abdomen and, because of extraintestinal cancers (see below), review of the reticuloendothelial system and skin, especially the anovaginal area. An explanation should be sought for recurrence of old symptoms or for development of new symptoms, particularly stricture, fistula, intestinal bleeding or weight loss, especially if these symptoms develop after a long period of quiescent disease. Excluded segments should be removed whenever re-operation is being performed. Patients with perianal abscesses, and internal and external fistulae should be considered to be at some risk for malignant transformation of these areas of chronic inflammation. A routine endoscopic surveillance program can be recommended for selected patients with longstanding (more than 10 years), universal disease, especially with early onset of CD. A controlled study should be designed to see if earlier diagnosis, leading to curative resection, could be made, utilizing multiple biopsies for dysplasia. In view of the occurrence of carcinoma in overtly normal appearing bowel, and in the colon and rectum in regional enteritis, biopsies of both normal and abnormal bowel would have to be made and examined for

dysplasia, carcinoma *in situ*, and infiltrating carcinoma. Biopsies would also have to be taken from elevated masses, adenomatous polyps, and especially from areas of stricture and fistula formation. Prophylactic colectomy should be advised if dysplasia develops in the absence of acute inflammation, and especially if dysplasia is found in the presence of an elevated mass. It remains to be seen whether small bowel enteroscopy will enable differentiation of benign from malignant strictures in the more proximal bowel.

The ratio of costs and risks to benefits has not been established for prophylactic colonoscopic surveillance, nor has an optimal surveillance regimen been determined. On an empirical basis, most such programs commence after 10 years of disease, often on an annual or biannual schedule. One could argue for earlier surveillance in view of the relatively high incidence of cancers in Crohn's disease during the first decade. Newer and more sensitive indicators of premalignancy, such as DNA flow cytometry, cell turnover kinetics, mucin histochemistry, lectin binding, or monoclonal antibody identification of antigenic tumor markers, may ultimately supplant routine histologic examination for dysplasia as more effective screening techniques.

### Indications for Surgery

#### A. Absolute

1. High-grade dysplasia or low-grade dysplasia found in patients in surveillance programs in the absence of acute inflammation, with or without a dysplasia-associated lesion or mass (DALM).
2. Carcinoma proven by endoscopic biopsy.
3. A stricture that cannot be passed.

#### B. Relative

1. An excluded loop; although patients often refuse surgery if quiescent.
2. A poorly compliant patient on whom regular surveillance cannot be done.
3. Surveillance is impossible in the high-risk patient because of multiple, large pseudopolyps or the difficulty of differentiating the dysplasia of adenomatous polyps.

#### C. Incidental

1. Patients may be operated on for other indications unrelated to the cancer, such as fulminating colitis, toxic megacolon or a cancer found pathologically.

### Principles of Surgery for Colorectal Cancer in IBD

The surgery for cancer in IBD is based on the principles which have evolved for cancer surgery in general: wide excision with lymphadenectomy, which should be carried out in conjunction with appropriate surgery for the inflammatory bowel disease.

In Crohn's colitis, except when the disease is extensive or universal, or severe perianal disease is present, segmental resection (SR) with reanastomosis is an option and frequently the preferred method of treatment. Although there is a high recurrence rate for colocolostomy, ileo-sigmoidostomy or ileo-proctostomy, these more limited resections allow the patient to retain the rectum, maintain intestinal continuity, and avoid a permanent ileostomy for variable periods of time. This is especially valuable in young patients. In CD, ileoanal pouch construction is at this time contraindicated. In indeterminate colitis, pelvic pouch construction may be successful with results almost as good as for ulcerative colitis (79).

Between 1960 and 1989, a total of 147 patients with cancer occurring in IBD were seen at The Mount Sinai Hospital in New York City. There were 30 with large bowel adenocarcinoma in CD, compared with 102 patients with CRC in UC (80). An additional 19 patients were seen with small bowel cancer (SBC) (15). The four groups of surgical procedures required for these patients included segmental resection (SR), total proctocolectomy (TPC) with end ileostomy or pelvic pouch (in UC only), subtotal colectomy (STC) with or without reanastomosis, and various palliative procedures (PP) including diversionary colostomy or ileostomy. The surgical procedures in our 130 patients with CC and UC complicated by CRC are listed in Table 1.

#### Segmental Resection (SR)

Segmental resection, right, left or distal abdominoperineal, was the preferred surgical therapy for Crohn's colorectal cancer, cancer occurring in what was often a segmental disease (Table 1). In this series, seven cases of colorectal cancer occurred in patients with regional enteritis localized to the small bowel (21). These cases were clearly ideal for SR, which was carried out in 14 patients, 46% of the series.

#### Total Proctocolectomy (TPC)

In CD, TPC is generally reserved for those patients with extensive or universal colitis, espe-

**TABLE 1**  
*Surgical Procedures for Colorectal Cancer in Inflammatory Bowel Disease*

	Ulcerative Colitis			Crohn's Disease		
	Subtotal n	Procedure n	%	Subtotal n	Procedure n	%
Total Proctocolectomy	51			5		
with ileostomy		43	43		5	17
with pelvic pouch		8	8		0	0
Subtotal Colectomy	25			5		
with ileostomy		11	11		4	14
with reanastomosis		14	14		1	3
Segmental Resection	14			14		
ileocolic		0	0		2	6
right colectomy		7	24		1	3
left colectomy		1	0		4	14
sigmoid/ant. res.		1	1		1	3
protect/Hartmann		0	0		1	3
abdomino-perineal		5	5		5	16
Palliative Procedure	5			5		
ileostomy		1	1		3	10*
colostomy/Hartmann	4	4**		2	7	
Unresectable						
inoperable/biopsy	4	4	4	1	1	3
laparotomy	1	1	1	0	0	0
<b>TOTAL</b>	<b>100</b>		<b>100</b>	<b>30</b>		<b>100</b>

\* One with proximal jejunojunostomy and ileoileostomy.

\*\* One following recurrence of a rectovesical fistula after a decade-long quiescent interval.

cially those with perianal disease in whom reconstruction of intestinal continuity is inadvisable. Although one-half of the patients with ulcerative colitis had TPC, only five (17%) of the Crohn's patients had primary TPC with a Brooke ileostomy.

#### Subtotal Colectomy (STC)

In CD complicated by carcinoma, STC was carried out in five (17%), a percentage somewhat less than the 25% in our UC patients. In only one was primary reanastomosis carried out. This is the preferred surgical procedure for UC patients who are ill, have severe active disease in addition to the cancer, are on steroids, are hypoalbuminemic and/or are severely anemic.

#### Palliative Procedures (PP)

Fewer than 5% of patients with CD or UC had cancers so advanced that they were inoperable. Palliative diversionary ostomy without resection was also necessary in an additional five (17%) of the patients with CD. The large number of unresectable cancers in CD was contributed to by the five patients with cancers in excluded

loops. In earlier years, this operation was carried out frequently at The Mount Sinai Hospital, but is no longer done today. In most other series, cancers in excluded loops are less common.

#### Small Bowel Cancer in Crohn's Enteritis

Segmental resection was the preferred surgical therapy for Crohn's enteritis in 79% of patients (Table 2). Unlike the patients with colorectal cancer, only one patient developed cancer in nondiseased bowel. The four patients requiring palliative diversion, or who were inoperable, constituted 21% of the total series, a similar proportion to the 6 of 30 patients (20%) with CDCRC. Of these cancers, five occurred in excluded loops (15, 16, 18, 19).

#### Reticuloendothelial Tumors

##### Lymphomas

Lymphomas, colonic or extraintestinal (52), do not occur commonly in either CD and UC. It has been suggested that the incidence is greater than what was expected (4). For intestinal lym-

**TABLE 2**  
*Surgical Procedures for Cancer in Small Bowel in Crohn's Disease*

	Subtotal n	Procedure n	%
Resection	15		79
small bowel resection		2	11
with ileostomy		1	5
with stricturoplasty	1	5	
ileocolic resection and reanastomosis	11	58	
Palliative Procedures	4		21
bypass/diversion			
ileotransverse colostomy	1	5	
jejunostomy		2	11
inoperable		1	5
TOTAL	19		100

phomas, local excision is required. This should be followed by radiotherapy when indicated, and chemotherapy, which is the definitive therapy for extraintestinal lymphoma (52).

### Leukemias

Leukemias are more common in ulcerative colitis than in Crohn's disease (4, 50) and occasionally may exacerbate the hemorrhage due to gastrointestinal ulceration. In one such patient with leukemia in CD, total proctocolectomy was required for massive gastrointestinal hemorrhage. Appropriate chemotherapy is necessary in all of these patients (50).

### Cancers of the Anorectum

Low rectal adenocarcinomas in both forms of IBD and squamous cell cancers of the anus in Crohn's disease, usually with perianal disease, are treated by radical abdominoperineal resection of the rectum including the sphincter muscles, when necessary and resectable (53, 81). Early or advanced squamous cell cancers may be treated by local excision, or by radical excision with or without radical lymphadenectomy prior to radiotherapy and chemotherapy.

### Peri-ileostomy Cancers

Cancers occurring at the site of an ileostomy are rare, but a number have been reported. Radical excision with transposition of the ileostomy is required (82).

### Stricture Cancers

Cancers occurring in association with strictures constitute a particularly difficult diagnostic problem both for CDCRC (69) and UCCRC (70), in which the incidence of malignancy in strictures is approximately 30% and 5% respectively. When the diagnosis of cancer cannot be ruled out, surgical resection is indicated.

Small bowel cancer should be ruled out in all patients with multiple strictures in jejunoileitis in whom stricturoplasty is performed (15).

### Cancer Occurring with Fistulae

This association has long been recognized (18, 19, 56, 59). Unfortunately such cancers are often unresectable. However, it is possible on occasion to carry out radical cancer "en bloc" resections, including the bowel on either side. This principle should be applied whenever the possibility of fistula cancer exists, even if unproven. If a complete cure is not possible, a longer period of palliation may be possible.

### Long-Term Outcome Following Surgery for Gastrointestinal Cancer in IBD

Survival following surgical resection is better in colorectal cancer than in small bowel cancer in Crohn's disease. Although early series suggested a poor long-term outcome for UCCRC, recent studies have shown that survival is similar to that for non-colitic colorectal cancer. We have found a 45% 5-year survival for CRC in CD, which increases to 56% if cancers in excluded loops are omitted (unpublished data). This is comparable to the 52% survival for our 100 UC patients (80). For small bowel cancer, survival is much poorer, at best 23% at 3 years (15). Mortality for cancers in excluded bowel was 100% for both small and large bowel (see Fig. 5) (15, unpublished data).

### Conclusions

Cancer in inflammatory bowel disease clearly increases in incidence in the intestinal tract and probably in certain extraintestinal sites as well. The absolute number of patients developing such malignancies are low compared to overall cancer rates in the general population, but because of higher relative risks, younger ages of onset, distinctive clinicopathological features, and difficulties in making a diagnosis, it is important that this complication of inflammatory bowel disease be widely appreciated. The prognosis today is no

worse for colorectal cancers in ulcerative colitis or Crohn's disease (except for those occurring in excluded bowel) than for *de novo* cancers of the large bowel, but it remains exceedingly poor for small bowel cancers in Crohn's disease. Surveillance can probably be advised for ulcerative colitis-related colorectal cancers, although there is still some doubt as to whether it will be cost-effective or how it will affect prognosis and survival. There is even greater doubt concerning its role in monitoring patients with Crohn's disease for either colorectal or small bowel cancers. A cooperative study of endoscopic surveillance to diagnose dysplasia or malignant change in the mucosa of patients with Crohn's disease is now essential. There is increasing evidence that it would be rational to carry out surveillance for patients clearly at increased risk, namely patients with: unresected colons; longstanding disease (>10 years); and extensive disease, particularly in those with early onset of their Crohn's disease. The surgery for cancer in inflammatory bowel disease is based on a combination of the general principles for the surgery of IBD without cancer and radical excisional cancer surgery. Resection of the mesentery and lymphadenectomy should be carried out according to general cancer principles. Postoperative survival for colorectal cancer is good, approximately 50%, compared with the poor, less than 23%, survival for small bowel cancer.

### References

1. Crohn BB, Rosenberg H. The sigmoidoscopic picture of chronic ulcerative colitis (non-specific). *Am J Med Sci* 1925; 170:220–227.
2. Wilks S. The morbid appearance of the intestine of Miss Banks. *The Medical Times & Gazette*. 1859; 2:264. Cited by: Goligher JC. In: *Ulcerative colitis*. 1968. Ref. 1: Cited by: Wilks S, Moxon W. In: *Lectures on pathological anatomy*. 2nd edition. London: Churchill; 1875.
3. Devroede GJ, Taylor WF, Sauer WG, et al. Cancer risk and life expectancy of children with ulcerative colitis. *N Engl J Med* 1971; 285:17–21.
4. Edwards FC, Truelove SC. The course and prognosis of ulcerative colitis. IV. Carcinoma of the colon. *Gut* 1964; 5:15–22.
5. Greenstein AJ, Sachar DB, Smith H, et al. Cancer in universal and left-sided ulcerative colitis: Factors determining risk. *Gastroenterology* 1979; 77:290–294.
6. Crohn BB, Ginzburg L, Oppenheimer GD. Regional ileitis. A pathologic and clinical entity. *JAMA* 1932; 99:1323–1329.
7. Warren S, Sommers SC. Cicatrizing enteritis (regional enteritis) as a pathologic entity: Analysis of one hundred and twenty cases. *Am J Pathol* 1948; 24:475–501.
8. Ginzburg L, Schneider KM, Dreizin DH, Levinson C. Carcinoma of the jejunum occurring in a case of regional enteritis. *Surgery* 1956; 39:347–351.
9. Greenstein AJ, Gennuso R, Sachar DB, et al. Extraintestinal cancers in inflammatory bowel disease. *Cancer* 1985; 56:2914–2921.
10. Dalziel TK. Chronic interstitial enteritis. *Br Med J* 1913; 2:1068–1070.
11. Nikias GW, Eisner T, Katz S, et al. Crohn's disease and colorectal carcinoma: Rectal cancer complicating longstanding active perianal disease. *Am J Gastroenterol* 1995; 90: 216–219.
12. Kornfeld P, Ginzburg L, Adlersberg D. Adenocarcinoma occurring in regional jejunitis. *Am J Med* 1957; 23: 493.
13. Frank JD, Shorey BA. Adenocarcinoma of the small bowel as a complication of Crohn's disease. *Gut* 1973; 14:120–124.
14. Greenstein AJ, Sachar DB, Smith H, et al. Patterns of neoplasia in Crohn's disease and ulcerative colitis. *Cancer* 1980; 46:403–407.
15. Ribeiro MB, Greenstein AJ, Heimann TM, et al. Adenocarcinoma of the small intestine in Crohn's disease. *Surg Gynecol Obstet* 1992; 173:343–350.
16. Brown N, Weinstein VA, Janowitz HD. Carcinoma of the ileum 25 years after bypass for regional enteritis: A case report. *Mt Sinai J Med* 1970; 27:675–678.
17. Zisk J, Shore JM, Rosoff L, Friedman NB. Regional ileitis complicated by adenocarcinoma of the ileum: A report of two cases. *Surgery* 1960; 47:970–974.
18. Senay E, Keohane M, Greenstein AJ. Small bowel carcinoma in Crohn's disease: Distinguishing features and risk factors. *Cancer* 1989; 63:360–363.
19. Greenstein AJ, Sachar D, Pucillo A, et al. Cancer in Crohn's disease after diversionary surgery: A report of seven carcinomas occurring in excluded bowel. *Am J Surg* 1978; 135:86–90.
20. Greenstein AJ, Sachar DB, Smith H, et al. A comparison of cancer risk in Crohn's disease and ulcerative colitis. *Cancer* 1981; 48:2742–2745.
21. Greenstein AJ, Meyers S, Szporn A, et al. Colorectal cancer in regional ileitis. *Q J Med* 1987; 62(237):33–40.
22. Clemmensen T, Johansen A. A case of Crohn's disease of the colon associated with adenocarcinoma extending from cardia to the anus. *Acta Pathol Microbiol Scand* 1972; 80:5–8.
23. Keighley MRB, Thompson H, Alexander-Williams J. Multifocal colonic carcinoma and Crohn's disease. *Surgery* 1975; 78:534–537.
24. Allan R, Steinberg DM, Dixon K, Cooke WT. Changes in the bidirectional sodium flux across the intestinal mucosa in Crohn's disease. *Gut* 1975; 15:201–204.
25. Crucio V. Rectal biopsy in Crohn's disease. *Rendiconti Gastroenterol* 1967; 4:73–76.
26. Ferguson R, Allan RN, Cooke WT. A study of the cellular infiltrate of the proximal jejunal mucosa in ulcerative colitis and Crohn's disease. *Gut* 1975; 15:205–208.
27. Goodman MJ, Skinner JM, Truelove SC. Abnormalities in the apparently normal bowel mucosa in Crohn's disease. *Lancet* 1976; 1:275–278.
28. Lenaerts C, Roy CC, Vaillancourt M, et al. High incidence of upper gastrointestinal tract involvement in children with Crohn's disease. *Pediatrics* 1989; 83:777–781.
29. Fielding JF, Prior P, Waterhouse JA, Cooke WT. Malignancy in Crohn's disease. *Scand J Gastroenterol* 1972; 7:3–7.
30. Alexander-Williams J. Inflammatory disease of the bowel. The risk of cancer. *Dis Colon Rectum* 1976; 19:579–581.
31. deDombal FT, Watts JMCK, Watkinson G, et al. Local complications of ulcerative colitis: Stricture, pseudopolyposis, and carcinoma of colon and rectum. *Br Med J* 1966; 1:1442–1447.
32. Greenstein AJ, Slater G, Heimann TM, et al. A Comparison of multiple synchronous colorectal cancer in ulcerative colitis, familial polyposis coli, and *de novo* cancer. *Ann Surg* 1986; 203:123–128.

33. Atwell JD, Duthie HL, Goligher JC. The outcome of Crohn's disease. *Br J Surg* 1965; 52:966–972.
34. Perrett AD, Truelove SC, Massarella GR. Crohn's disease and carcinoma of colon. *Br Med J* 1968; 2:466–468.
35. Weedon DD, Shorter RG, Ilstrup DM, et al. Crohn's disease and cancer. *New Engl J Med* 1973; 289:1099–1102.
36. Buchmann P, Allan RN, Thompson H, Alexander-Williams J. Carcinoma in a rectovaginal fistula in a patient with Crohn's disease. *Am J Surg* 1980; 140:462–463.
37. Darke SG, Parks AG, Grogono JL, Pollock DJ. Adenocarcinoma and Crohn's disease: A report of two cases and analysis of the literature. *Br J Surg* 1973; 60:169–175.
38. Gyde SN, Prior P, Macartney JC, et al. Malignancy in Crohn's disease. *Gut* 1980; 21:1024–1029.
39. Eckbom A, Helmick C, Zack M, Adami HO. Increased risk of large bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990; 336:357–359.
40. Gillen CD, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: A comparison of the colorectal cancer risk in extensive colitis. *Gut* 1994; 35:1590–1592.
41. Gollop JH, Phillips SF, Melton LJ, Zinsmeister AR. Epidemiologic aspects of Crohn's disease: A population based study in Olmsted County, Minnesota, 1943–1982. *Gut* 1988; 29:49–56.
42. Kvist N, Jacobsen O, Norgaard P, et al. Malignancy in Crohn's disease. *Scand J Gastroenterol* 1986; 21:82–86.
43. Fireman Z, Grossman A, Lilos P, et al. Intestinal cancer in patients with Crohn's disease. A population study in central Israel. *Scand J Gastroenterol* 1989; 24:346–350.
44. Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993; 105:1716–1723.
45. Persson P-G, Karlen P, Bernell O, et al. Crohn's disease and cancer: A population-based cohort study. *Gastroenterology* 1994; 107:1675–1679.
46. Sachar DB. Cancer in Crohn's disease: Dispelling the myths. *Gut* 1994; 35:1507–1508.
47. Gillen CD, Andrews HA, Prior P, Allan RN. Crohn's disease and colorectal cancer. *Gut* 1994; 35:651–656.
48. Lennard-Jones JE, Stalder GA. Prognosis after resection of chronic regional ileitis. *Gut* 1967; 8:332–336.
49. Prior P, Gyde SN, Macartney JC, et al. Cancer morbidity in ulcerative colitis. *Gut* 1982; 23:490–497.
50. Fabry TL, Sachar DB, Janowitz HD. Acute myelogenous leukemia in patients with ulcerative colitis. *J Clin Gastroenterol* 1980; 2:225–227.
51. Hanauer SB, Wong KK, Frank PH, et al. Acute leukemia following inflammatory bowel disease. *Dig Dis Sci* 1982; 27:545–548.
52. Greenstein AJ, Mullin GE, Strauchen JA, et al. Lymphoma in inflammatory bowel disease: A study of 9 cases. *Cancer* 1992; 69:1119–1123.
53. Slater G, Greenstein AJ, Aufses AH, Jr. Anal carcinoma in patients with Crohn's disease. *Ann Surg* 1984; 199:348–350.
54. Greenstein AJ, Sachar DB, Shafir M, et al. Malignant melanoma in inflammatory bowel disease. *Am J Gastroenterol* 1987; 82:964.
55. Penn I. The occurrence of cancer in immune deficiencies. *Curr Probl Cancer* 1982; 6:28–43.
56. Lightdale CJ, Sternberg SS, Posner G, Sherlock P. Carcinoma complicating Crohn's disease: Report of seven cases and review of the literature. *Am J Med* 1975; 59:262–268.
57. Buchmann P, Allan RN, Thompson H, Alexander-Williams J. Carcinoma in a rectovaginal fistula in a patient with Crohn's disease. *Am J Surg* 1980; 140:462–463.
58. Sher ME, Bauer JJ, Gelernt. Surgical repair of rectovaginal fistulas in patients with Crohn's disease: Transvaginal approach. *Dis Colon Rectum* 1991; 34:641–648.
59. Church JM, Weakley FI, Fazio VW, et al. The relationship between fistulas in Crohn's disease and associated carcinoma. Report of four cases and review of the literature. *Dis Colon Rectum* 1985; 28: 361–366.
60. Zinkin LD, Brandwein C. Adenocarcinoma in Crohn's colitis. *Dis Colon Rectum* 1980; 23: 115–117.
61. Hamilton SR. Colorectal carcinoma in patients with Crohn's disease. *Gastroenterology* 1985; 89:398–407.
62. Kyle J, Ewen SWB. Two types of colorectal carcinoma in Crohn's disease. *Ann R Coll Surg Engl* 1992; 74:387–390.
63. Hoffman JP, Taft DA, Wheelis RF, Walker JH. Adenocarcinoma in regional enteritis of the small intestine. *Arch Surg* 1977; 112:606–611.
64. Fresco D, Lazarus SS, Dotan J, Reingold M. Early presentation of carcinoma of the small bowel in Crohn's disease ('Crohn's carcinoma'): Case reports and review of the literature. *Gastroenterology* 1982; 82:783–789.
65. Fleming KA, Pollock AC. A case of 'Crohn's carcinoma.' *Gut* 1975; 16:533–537.
66. Morson BC, Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. *Gut* 1967; 8:423–434.
67. Thompson EM, Clayden G, Price AB. Cancer in Crohn's disease — an 'occult' malignancy. *Histopathology* 1983; 7:365–376.
68. Warren R, Barwick KW. Crohn's colitis with carcinoma and dysplasia: Report of a case and review of 100 small and large bowel resections for Crohn's disease to detect incidence of dysplasia. *Am J Surg Pathol* 1983; 7:151–159.
69. Yamazaki Y, Ribeiro MB, Sachar DB, et al. Malignant colorectal strictures in Crohn's disease. *Am J Gastroenterol* 1991; 86:882–885.
70. Gumaste V, Sachar DB, Greenstein AJ. Benign and malignant colorectal strictures in ulcerative colitis. *Gut* 1992; 33:938–941.
71. Cooper DJ, Weinstein MA, Korelitz BI. Complications of Crohn's disease predisposing to dysplasia and cancer of the intestinal tract: Considerations of a surveillance program. *J Clin Gastroenterol* 1984; 6:217–224.
72. Korelitz BI. Carcinoma of the intestinal tract in Crohn's disease: Results of a survey conducted by the National Foundation for Ileitis and Colitis. *Am J Gastroenterol* 1983; 78:44–46.
73. Shorter RG. Risks of intestinal cancer in Crohn's disease. *Dis Colon Rectum* 1983; 26:686–689.
74. Butt JH, Morson BC. Dysplasia and cancer in inflammatory bowel disease [editorial]. *Gastroenterology* 1981; 80: 865–868.
75. Butt JH, Lennard-Jones JE, Ritchie JK. A practical approach to the risk of cancer in inflammatory bowel disease. *Med Clin North Am* 1980; 64:1203–1220.
76. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: Standardized classification with provisional clinical applications. *Hum Pathol* 1983; 14:931–968.
77. Kim U, Klein M, Baek S, et al. Carcinoma of the small intestine in Crohn's disease — occurrence in a bypassed loop. *Mt Sinai J Med* 1976; 43:461–466.
78. Greenstein AJ, Sachar DB, Kark AE. Stricture of the anorectum in Crohn's disease involving the colon. *Ann Surg* 1975; 181:207–212.
79. McIntyre PB, Pemberton JH, Wolff BG, et al. Indeterminate colitis: Long-term outcome in patients after ileal pouch-anal anastomosis. *Dis Colon Rectum* 1995; 38:51–54.
80. Sugita A, Greenstein AJ, Ribeiro MB, et al. Survival with colorectal cancer in ulcerative colitis: A study of 102 cases. *Ann Surg* 1993; 218:189–195.
81. Connell WR, Sheffield MA, Kamm MA, et al. Lower gastrointestinal malignancy in Crohn's disease. *Gut* 1994; 35:347–352.
82. Suarez V, Alexander-Williams J, O'Connor HJ, et al. Carcinoma developing in ileostomies after 25 or more years. *Gastroenterology* 1988; 95:205–208.